synapisms. All treatments and medication were grouped to disturb the patient as infrequently as possible.

In evaluating treatment, it seemed to us that the nursing and oto-laryngological services were of first importance; that cool air with a humidity of 75% was particularly beneficial; that adequate fluid intake was important; that hypertonic plasma was of doubtful value; and that penicillin and sulfonamides, while indicated because of the seriousness of the disease, were very disappointing in altering the course.

NASAL MEDICATION IN SINUSITIS*

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IN the light of recent knowledge, nasal medication in upper respiratory infections has undergone a change in the past few years. Greater interest has been stimulated in this subject due in great measure to the contributions of Proetz,[1] Hilding,[2] Lierle and Moore,[3] Walsh and Cannon.[4] When Proetz introduced his displacement method in 1926, the diagnosis and treatment of sinusitis was placed on an entirely new level. He showed how simply fluid could enter the sinuses by posture and intermittent suction. A few years later, Hilding demonstrated the direction and flow of mucus through the nose and its relation to ciliary activity.

Following these important advances Lierle and Moore pointed out that ephedrine, up to 3% in normal saline caused no damage to the cilia or to the epithelium of the nasal mucosa. They also demonstrated the harmful effects on the mucous membrane of nearly all the drugs used in sprays and droppers, including adrenalin, cocaine, silver salts and volatile oils. Even tap water and distilled water caused a definite slowing of the ciliary beat when applied to the mucous membrane of the upper respiratory tract. Seven years ago, Walsh and Cannon drew attention to the fact that many nasal drops or sprays caused permanent damage to lung tissue. They also showed that on aspiration silver salt preparations were more harmful to bronchial epithelium than mineral oil. On the nasal mucous membrane they also have an irritating effect in all probability due to their high alkaline pH value. Although 10% silver solutions do not appear to injure the cilia of the nose, they tend to upset the normal flow of mucus. This is thought to be due to the clumping effect of the precipitated silver protein which interferes with ciliary movement.

Mineral oil preparations containing menthol, eucalyptol and camphor have been prescribed by the medical profession for years in the belief that they clear the head. This was disproved by Fox[5] who showed that solutions as weak as 1% produce a swelling of the mucous membrane which reduces the volume of air through the nose to about one-half. Although there is a sensation of increased patency, this is not actually the case. Since it has been shown that oily solutions containing 5% menthol, eucalyptol and camphor sprayed into the nose daily have a definitely destructive effect on nasal mucosa,[6] their popularity has waned.

Liquid paraffin as a base for nasal medication does not actually reach the cilia but remains on the surface of the layer of mucus.[7] Although it does not cause any chemical harm, oil does not mix with mucus but lies as a heavy blanket on the mucous membrane and by its weight alone interferes with ciliary movement. The danger of pneumonia following the instillation of oily drops in children has also become recognized.

In view of these findings the trend in recent years has been toward nasal medication which does not disturb the normal physiology of the nose. One of the most important physio-chemical properties of nasal secretion appears to be its hydrogen ion concentrations. Eleven years ago Tweedie[8] attempted to show the relation of the bacterial flora of the nose to the pH value of nasal mucus. He found that in all patients in whom the pH value was 6.5 or below, that is slightly acid, cultures from the nose were negative. In the presence of inflammation when the pH was raised to the alkaline side, that is, above pH 7, organisms were usually found. From this he concludes that an acid reaction is inhibitory to the growth of pathogenic bacteria. According to Negus,[9] the beat of nasal cilia is

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greatly increased in an alkaline medium but is slowed down when the pH of the nose is acid—6.4 or less.

Four years ago Fabricant[10, 11, 12] emphasized the importance of the pH value in the treatment of nasal infections. He devised a method of obtaining pH readings of nasal secretions *in situ*. Previous to this, mucus was collected in containers and when exposed to the air underwent changes which made the readings inaccurate. As a result of his findings, Fabricant noted clinically that in normal cases the nasal pH varied from 5.5 to 6.5. This is slightly lower than the estimates obtained by the above older methods. Nungester and Atkinson[13] reported a somewhat different method of estimating the pH of nasal mucosa *in situ* and their readings were slightly higher. According to their findings, the normal pH is 6.6 to 7.6 and that patients with acute rhinitis have exactly the same pH value. They concluded that the mean pH value in the common cold is essentially that of the normal nasal mucosa.

Recently Parkinson[14] attempted to explain the evident confusion in the results for the determination of intranasal pH. He stated that within the nasal chambers are two distinct sources of hydrogen ion concentration: living tissue, that is nasal mucous membrane, and non-living secretion or nasal mucus. Living nasal mucosa under the control of body mechanisms contains fluid which maintains standard physical properties. On the other hand, nasal secretion while derived from body fluid is non-living and is neither standard or constant. "Thus there are in contiguity two intranasal fluids: body fluid within the tissue with physical characteristics controlled and constant, and secretion on the tissue surface with values uncontrolled and ever-changing."

An intranasal electrode lies in contact with the nasal mucous membrane and nasal secretion so that the pH determinations *in situ* give the combined hydrogen ion value of nasal mucosa and nasal secretion. Apparently it seems impractical at present to make separate readings, so that the term intranasal pH would appear sufficient. It is hoped that in the near future with improved methods more uniform findings will result.

The pH value depends on a number of factors. Temperature changes influence it. For instance, cold tends to make the secretion alkaline while heat causes a drift towards acidity. During an acute cold or sinusitis as well as in the presence of an allergic attack the pH readings of nasal secretions are high, *i.e.*, alkaline. These facts are borne out by Hilding[15] who found that the pH became more alkaline during the first four days of an acute head cold. Buhrmester[16] also noted that secretion from patients suffering from nasal allergy were as a rule highly alkaline.

Nasal pH also varies with rest and sleep and throughout the day. Rest in bed and sleep tend to produce an acid reaction in nasal pH and this is more marked at night than during the day. Atlhough it is sometimes difficult to persuade a patient in the early stages of an acute rhinitis or sinusitis to remain in bed, theoretically this appears to be sound advice. Apart from the danger of spreading the infection, rest and heat alone tend to reduce the high alkalinity of the nasal secretion to the normal slightly acid level.

Considering that the vast majority of acute sinus infections, excluding allergy, originate from the common cold, the early treatment of this condition is important. The organisms most frequently found in the nose during an acute coryza or nasopharyngitis are the beta hæmolytic streptococci, pneumococci, and *H. influenzæ*, although the predominating organism varies from year to year.[17] Fortunately from a rhinologist's point of view, the secondary invaders which produce sinusitis and ear complications—streptococci, staphylococci and pneumococci — are controlled by chemotherapy.

In view of the miraculous results obtained with the sulfonamides by mouth and intravenously in cases of pneumonia, septicæmia, streptococcic infections, etc., it was thought that locally they would be just as effective. In open wounds, such as operative fields, sulfonamide powder or solution on dressings seems beneficial. The local use of sulfonamides in the nose in powder form or in solution combined with vasoconstrictors has been tried with varying success. With an intact nasal mucous membrane, it is doubtful whether the sulfonamides have sufficient bacteriostatic action to be effective. The absorption into the blood stream from an inflamed but intact mucous membrane is also very limited.

A series of cases of acute sinusitis were treated by nasal instillations of 5% sulfathiazole

three times a day for a ten-day period. Blood levels were then taken but it seemed impossible to raise the concentration above 0.5 mgm. %.

Since the advent of the sulfonamides, various reports have appeared in the literature concerning their therapeutic value in acute and subacute rhinitis and sinusitis. According to Livingston[18] oral sulfonamide therapy in acute nasal sinusitis is as effective as in cases of acute otitic infections. "In conjunction with other indicated measures, sulfonamides usually effect quicker relief, a shorter course, and less tendency to complications than when not used." Concerning the local effect of the sulfonamides in the nose, opinions at present vary considerably. Many writers recommend the sulfa compounds combined with a mild shrinking agent in an isotonic solution, and are enthusiastic over their results. Others are equally satisfied with a weak vasoconstrictor in normal saline without any added medication as long as ventilation and drainage are maintained. In a recent article on the local use of sulfa solution in the nose, Whalen[19] concluded that the beneficial results were due more to the accompanying vasoconstrictors than the sulfonamides. Since it has been shown that certain of the salts of sulfathiazole, particularly sodium, have a deleterious effect on the cilia and nasal mucous membrane even in concentrations as low as 5%,[20] there has been a tendency to use sulfonamide solutions of 2 and 3%. Powdered sulfathiazole, sulfadiazine and the microcrystals in 5% saline solutions do not appear to exert any destructive action on the cilia or nasal mucosa. However, in the light of our present knowledge, it seems reasonable to assume that solutions for nasal medication should be isotonic, slightly acid, that is with a pH between 5.5 and 6.5 and not interfere with ciliary activity or injure the mucous membrane.

There appears to be a difference of opinion in applying solutions to the nose. Recently Butler and Ivy[21] described the methods and merits of nasal medication. They compared nose drops with sprays and volatile inhalers and concluded that, "the effects on the nasal mucosa produced by repeated administration of inhalers and sprays are similar, and both produced far less pathological change than that resulting from the use of nasal drops." By means of the inhaler and spray a thin layer of the drug is spread over a greater area of mucous membrane and is therefore more effective in reducing nasal obstruction. However, in acute cases where the turbinates are inflamed and swollen, it is doubtful whether solutions from nasal sprays reach the ostia of the sinuses.

On the other hand, unless instructions are given by the surgeon, nose drops applied by patients usually spread over the lower half of the nose and do not enter the middle and superior meatuses where shrinkage is important. In this way certain localized areas are blanched by vasoconstrictors especially on the inferior turbinates and if this is repeated over long periods, destructive changes occur which lead to permanent damage of the mucous membrane.

Now that penicillin is available for civilian use, it opens a new field to the otolaryngologist. Since the discovery of the antibacterial properties of penicillin and gramicidin, a by-product of tyrothricin obtained from soil bacteria, great strides have been made.

These two preparations have distinct advantages over the sulfonamides with few disadvantages. Gramicidin as the name suggests is effective against many Gram-positive organisms such as pneumococcus and some forms of streptococcus and staphylococcus. Gram-negative organisms such as *B. Friedlander* and *H. influenzæ*, *B. coli* and *B. proteus* are not acted upon by the mould. However, gramicidin has certain limitations, as it is toxic when injected intramuscularly or intravenously and must be used as a topical application. It is insoluble in water and as it is not absorbed it must be in direct contact with organisms to be at all effective. It comes in sealed ampoules, in stable form, so that a 2% solution is readily made up (8 minims to one ounce of distilled water). This solution remains active for at least three weeks and is said to be effective when used in nose drops, spray or displacement where the offending organism is sensitive to gramicidin.

In using gramicidin (tyrothricin) and penicillin, accurate bacteriological findings are of paramount importance. For instance, certain strains of pneumococcus, streptococcus and staphylococcus pyogenes are not acted upon by gramicidin but are sensitive to penicillin or the sulfonamides. At times it is necessary to use a combination of two or all three to destroy a Gram-positive infection. Some aerobic and anaerobic streptococci and pneumococci are affected by tyrothricin while certain types of staphylococci are resistant. Many of these are peni-

cillin-sensitive but in the same way some are not in the least influenced by penicillin.

Repeated cultures and the importance of the rhinologist and bacteriologist working together at once becomes self-evident.

Penicillin on the other hand has a wider range of usefulness against Gram-positive organisms without the disagreeable side effects of the sulfonamides. It is soluble in water, is quite innocuous even in large doses, and can be used locally or given intramuscularly, intravenously or intrathecally. Recently it has successfully been given by mouth. In the proper dilution it is non-irritating to mucous membrane and does not injure the ciliated epithelium of the nose. Various writers have stressed the fact that solutions of penicillin must be fresh, that they lose their effectiveness after a week or ten days and that they should be kept in the ice-box. Experience with penicillin by the displacement method in the nose for the past year has given remarkably good results. During that time, we have on many occasions kept solutions for over two weeks—often at room temperature—and still found them potent to destroy *Strep. hæmolyticus,* according to the bacteriologist. This is important, as it is not always convenient to procure fresh solutions every few days and some forms of streptococci are very resistant, requiring the continuous action of penicillin for at least ten days to be effective. This has been shown in cases of closed abscess cavities where it is possible to maintain a high penicillin concentration. The time required to sterilize pus varies, depending on the causative organism. For instance, the pneumococcus is very sensitive and is destroyed in about forty-eight hours. About the same time is necessary to kill *Strep. hæmolyticus.* On the other hand, *Staph. pyogenes* is more resistant, as it requires ten days to two weeks in order to free a cavity of this infection. Two other organisms might be mentioned although they are rarely found in the nose. The meningococcus and gonococcus are very sensitive to penicillin and are easily destroyed in thirty-six to forty-eight hours. This time factor is very important as the length of treatment is influenced by the predominating organism present in the nose.

According to Proetz fluid instilled into the nose by the displacement method remains in the sinuses from twenty-four to ninety-six hours or longer, depending upon the distribution of the cells, the position of the ostia, the viscosity of the fluid, etc. We have had excellent results using penicillin by the displacement method every forty-eight hours for four, six, eight or ten treatments, depending upon the offending organism reported by the bacteriologist.

The following case indicates the efficacy of this form of therapy:

A man of 61 reported to his physician concerning a severe cough which had persisted for nearly six months. At times he would be seized by a sudden spasm and feel so distressed that he seemed unable to breathe. The results of the general physical examination proved negative, but a roentgenogram of the chest showed some aneurysmal dilatation of the arch of the aorta. The aneurysm was not considered sufficient to account for the cough, and he was referred for an otolaryngological consultation. Examination of the ears revealed no abnormality and hearing was normal on the two sides. The nose showed a mild degree of reddening of the mucous membrane but no evidence of pus or polypi. The septum was in the midline, and on transillumination, the sinuses appeared equally clear throughout. According to his past history, there were no indications of frequent colds or sinusitis, although the roentgenogram showed a slightly thickened lining of the left antrum, the other sinuses being clear. The pharynx and nasopharynx were normal, but the larynx showed a definite lagging of the left vocal cord, the right moving freely. Material taken from the middle meatus of each side and the nasopharynx on swabs produced a heavy growth of *Staph. aureus* in pure culture on three occasions. Staphylococcus toxoid and autogenous vaccines gave severe local reactions but did not influence the cough. The patient became slightly anæmic and began to tire easily, partly from the coughing spasms but also, it was thought, from the low-grade infection present.

On reviewing the case two facts seemed important. There was constant mild inflammation of the nasal mucous membrane, and repeated cultures of material from the middle meatus on each side and from the nasopharynx showed a heavy growth of *Staph. aureus,* practically in pure culture.

It was decided to use penicillin locally in the nose, as this seemed to be the source of infection. However, when nasal medication is accomplished by means of a dropper with the head in the dependent position, the drug used disappears into the nasopharynx within a few minutes and therefore loses its effect quickly. In contrast, fluid instilled into the sinuses by displacing the air remains, as a rule, for one to three days. It was therefore decided to try the displacement method in order that the drug might remain in the sinuses as long as possible. A penicillin salt was dissolved in sterile isotonic solution of sodium chloride to a strength of 10,000 units of the active substance per cubic centimetre. This solution was kept in rubber-capped bottles in the ice-box. After the patient's nose had been sprayed and the mucosa shrunk with a 5 to 8% solution of cocaine hydrochloride, he was placed on a table with his head hyperextended over the edge as described by Proetz. He was then asked to roll slightly on his side with the nose turned upward so the fluid could not run out. A sterile nasal dropper was filled three times with the solution of penicillin and emptied into the lower nostril. The dropper held 1 c.c., hence 3 c.c. was used. Intermittent negative pressure from a rotary pump was applied to the lower nostril through an olive tip while a finger closed the upper nostril. The patient was instructed to repeat the letter K in order to close the pharynx. After applying alternate suction ten or twelve times to displace the air and get the solution into the sinuses, another dropperful or two were instilled and the suction repeated. The head was then turned to the other side and the other nostril treated in the same way. The whole procedure required only a minute or two.

On returning to the upright position, the patient noticed little taste, the solution of necessity being in the sinuses. He was cautioned against blowing his nose for at least an hour or two.

This procedure was repeated on four occasions at forty-eight hour intervals, and two days later material was taken with swabs and cultured. Forty-eight hours between treatments was considered sufficient, as previous roentgen films showed iodized poppy seed oil 40% to be retained in the sinuses for at least that length of time. On examining the cultures, to our surprise we found that the left side was free of organisms but that a few colonies of staphylococcus appeared on the plate inoculated with material from the right middle meatus.

There was still a heavy growth in pure culture on the plate inoculated with material from the nasopharynx. Displacement was again carried out on four occasions at forty-eight hour intervals. On the last two occasions, the head was hyperextended but kept in the midline in order to fill the posterior cells of the ethmoid and the sphenoid sinus as well as the nasopharynx.

This time cultures of material from the right and left middle meatuses were sterile but there were still a few colonies of staphylococci on the plate inoculated with material from the nasopharynx. In the meantime the patient reported that the severe paroxysms of cough had completely disappeared; he was eating and sleeping better and his general condition was greatly improved. A third series of four treatments was given in the same way as the first, and the cultures made four days later of material from both middle meatuses and the nasopharynx proved to be sterile.

One or two points that were brought out in this case should be mentioned. Although the nose was cocainized well with a 5 to 8% solution, the patient complained of a burning discomfort which involved the nose and the eyes. This lasted for an hour or so after each treatment and has been mentioned by other writers who reported cases in which penicillin was used locally in wounds. A solution of a penicillin salt in 1% solution of tetracaine hydrochloride was made up and found to be satisfactory. The anæsthetic effect of tetracaine does not in any way interfere with the action of penicillin. The patient at once remarked on the diminished irritation, as have other patients treated more recently in a similar manner.

There might be some criticism of the shrinking of the nasal mucous membrane with a 5 to 8% solution of cocaine on account of the subsequent engorgement with narrowing of the ostiums of the sinuses. This we considered beneficial, as the solution containing penicillin was thereby retained in these cavities for a longer period.

In the case here reported dramatic results were seen from this form of treatment, which convincingly substantiates the opinion that a low-grade infection was one of the determining factors in the production of the cough. It will be interesting to observe whether subsequent infections of the upper respiratory tract again initiate the cough.

Since such a striking improvement was witnessed in this patient, many others have been treated in the same way. In young children as well as in elderly adults, the results have been equally good. Sinus infections in which the offending organism was pneumococcus, streptococcus or *Staph. pyogenes* and which were not complicated with allergic manifestations have responded readily to this form of treatment. A recent case of low-grade sinusitis in a boy of ten years caused by *Neisseria catarrhalis* cleared up after penicillin had been introduced into the sinuses on four occasions by the displacement method. Material on a swab taken from the middle meatus gave a profuse growth of this organism, almost in pure culture. We have been unable to find in the literature any reference to penicillin acting on *N. catarrhalis*, but basing our therapy on the close resemblance of this organism to the gonococcus and the meningococcus, we tried it, with gratifying results. Thus we have in penicillin an agent which is nontoxic, is isotonic, is slightly acid with a pH of 6.5, which does not interfere with ciliary streaming and does not injure the nasal mucous membrane.

Contrary to the suggestion of Garrod,[22] there is no clinical evidence whatever that overdosage with penicillin either systemically or topically has ever been observed.

Fortunately for the rhinologist, a great proportion of the infections of the upper respiratory tract involving the sinuses are caused by Gram-positive organisms and many of these respond to penicillin therapy.

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